

REMARKS

I. Status of Claims

The instant invention presently contains Claims 1, 3-6, 19-22, 35 and 37 and 44.

Claim 44 is newly presented.

Claims 2, 23-34 and 36 have been withdrawn.

Claims 1, 3-6, 19-22, 35 and 37 stand rejected.

The Examiner's remarks on cancellation of withdrawn claims are noted.

Withdrawn claims will be cancelled when allowable subject matter is indicated.

II. Amendment of Claims 1 and 38

Claims 1 and 38 have been amended to include the condition of "gas-free" to distinguish the instant invention from the gas-filled liposomes referenced in US. Pat. No 5,770,222 to Unger *et al.*, col. 5, lines 11-12 (at least 10% of the interior volume being gas). This amendment is a proper exclusion from claimed subject matter. See, *In re Johnson*, 558 F.2d 1008, 1017 (CCPA 1977) (the court should not let form triumph over substance by substantially eliminating the right of an applicant to retreat to an otherwise patentable species merely because he erroneously thought he was first with the genus when he filed.); *Ex parte Parks*, 30 USPQ2d 1234, 1236 (Bd. Pat. App. & Inter. 1993) (original disclosure conveys to one of ordinary skill in the art the absence of the excluded condition).

Independent Claim 38 has been amended to exclude nucleic acids from the scope of active substances. Claim 42, dependent on Claim 38, has been amended to clarify the limited scope of active substance. As noted above, such amendment is a proper exclusion from claimed subject matter. See, *In re Johnson*, 558 F.2d 1008, 1017 (CCPA 1977); *Ex parte Parks*, 30 USPQ2d 1234, 1236 (Bd. Pat. App. & Inter. 1993).

Claim 1 has been further amended to recite "consisting of" for "comprising."

New Claim 44 tracks Claim 1, here presented as a "use" claim.

Claims 1, 38, and 44 specify that delayed release be burst release avoiding. Support for this amendment is found throughout the application with particular reference to paragraph 15.

III. Claim Objections

The Examiner objected to claim 38 as to the phrase “comprising the steps of.” Applicant has amended Claim 38 accordingly to clarify a second step. Applicant believes that this objection is met.

IV. Claims 38, 40 and 42 are rejected under 35 USC § 102(b)

The Examiner initially rejected claims 38, 40 and 42 under 35 USC § 102(e) as being anticipated by U.S. Patent No. 7,008,791 to Gregoriadis *et al.*, (“Gregoriadis”). However, in discussion with Thomas M. Saunders on July 16, and 17, 2009, the Examiner indicated that 35 USC § 102(b) would also have been a basis for rejection if the international publication had been cited as the basis of rejection. Applicant respectfully traverses this rejection. The courtesy of Examiner Nguyen’s telephone calls are gratefully acknowledged.

A. The Rejection:

Gregoriadis is presented an *oral* vaccine formulation disclosed as various cationic lipid components, cholesterol and entrapping “a DNA encoding an antigen,” “nucleic acid may be complexed with liposomes,” and “the nucleic acid is at least partially entrapped.” Office Action of May 1, 2009, page 4, last paragraph. Further the Examiner states that “The teachings of Gregoriadis *et al* meet every limitation of the instant claims as written. Office Action of May 1, 2009, page 5, second paragraph. The Advisory Action dated September 9, 2009 draws attention to Claims 38, 40 and 42 as including not excluding nucleic acid. As amended, this rejection is met. Further, Gregoriadis is directed to oral drug delivery.

B. Applicant’s Invention:

Applicant claims “depot system, for burst release avoiding delayed release of active substances.” Applicant respectfully emphasizes that the depot system is (i) an injectable system (see, the Abstract), (ii) characterized by burst release avoiding delayed release, and that (iii) proteins and peptides are not nucleic acids (which are excluded). New Claim 44 contains these limitations.

The Deficiency of Gregoriadis:

Gregoriadis does not teach an injectable formulation. Gregoriadis does not teach burst release avoiding delayed release. Gregoriadis does not teach the use of claimed “protein or peptide active” substances in a depot system. Gregoriadis offers nothing to motivate a

researcher looking for a sustained release device for extracellular cargoes to consider an oral formulation. Gregoriadis is not and cannot be anticipatory of the claimed invention. Applicant requests that the rejection be withdrawn.

V. Claims 38 through 43 are rejected under 35 USC § 102(b)

The Examiner rejected claims 38 through 43 under 35 USC § 102(b) as being anticipated by U.S. Patent No. 5,770,222 to Unger *et al.*, ("Unger"). Applicant respectfully traverses this rejection.

A. The Rejection:

Unger is cited as a drug delivery system with gas-filled liposomes and some level of impermeability. Unger is also cited for having "at least about 75% or at least about 90% of the therapeutic drug and gas content of the liposomes remain with the liposomes because of their impermeability until they reach the internal region of a patient to be targeted and ultrasound is applied." Office Action of May 1, 2009, at 5. The materials in Unger are administered in no particular fashion (col. 16, lines 29-44) being designed to aggregate at a certain tissue and are then be ruptured by external energy.

B. Applicant's Invention:

Applicant's invention is (i) a *depot* system including (ii) "*burst release avoiding delayed release of active substances*." The depot condition addresses localization of the liposomes. "Burst release avoiding delayed release," as the term is used by Applicant references, "depot systems which avoid 'burst release' of active substance or, if therapeutically indicated, achieve rapid initial partial release of active substance, followed by a sustained release of active substance." Specification, ¶15. This presents two aspects. First, there is no burst release." Second, even if there is a rapid initial release of drug, it is followed by a long release profile.

As amended, Claim 38 includes the condition of "gas-free" as does Claims 39 through 43 dependent on Claim 38. It is proper to exclude gas filled liposomes by amendment. See, *In re Johnson*, 558 F.2d 1008, 1017 (CCPA 1977) (the court should not let form triumph over substance by substantially eliminating the right of an applicant to retreat to an otherwise patentable species merely because he erroneously thought he was first with the genus when he filed); *Ex parte Parks*, 30 USPQ2d 1234, 1236 (Bd. Pat. App. & Inter. 1993) (original disclosure conveys to one of ordinary skill in the art the absence of the excluded condition).

C. The Deficiency of Unger

Unger is not a “burst release avoiding delayed release” system as the term is used by the Applicant. The claimed “burst release avoiding delayed release” excludes burst release. It is respectfully submitted there can be no anticipation based on Unger. Unger discloses a period of *no release* followed by a *burst release*. This is not to be equivalent to Applicant’s claimed burst release avoiding delayed release depot system. Unger discloses having “at least about 75% or at least about 90% of the therapeutic drug and gas content of the liposomes remain with the liposomes because of their impermeability until they reach the internal region of a patient to be targeted and ultrasound is applied” – nothing but burst. Unger’s burst release condition is emphasized with reference to Unger, col. 2, lines 12-17:

Once the microspheres have been introduced into the patient's body, a therapeutic compound may be targeted to specific tissues through the use of sonic energy, which is directed to the target area and causes the *microspheres to rupture* and release the therapeutic compound. (emphasis added)

And col. 2, lines 22-2:9

The invention also contemplates methods for the *controlled delivery* of therapeutic compounds to a region of a patient comprising: (i) administering to the patient gas-filled microspheres comprising a therapeutic compound; (ii) monitoring the microspheres using ultrasound to determine the presence of the microspheres in the region; and (iii) *rupturing the microspheres using ultrasound to release the therapeutic compound in the region*. (emphasis added)

Unger’s “controlled delivery” is not Applicant’s “burst release avoiding delayed release.”

Rupture of the liposomes can only result in burst release without the possibility of a continuing release.

As amended, Claims 38 through 43 and new Claim 44 are distinct and not anticipated by Unger. The teaching of Unger is contrary to the claimed depot system of Applicant. Further, Unger fails as a single source disclosing all of the claimed elements arranged as in the claim. *Richardson v. Suzuki Motor Co.* 886 F 2d 1226, 1239 (Fed.Cir. 1989). Applicant requests that the rejection be withdrawn.

VI. Obligations under 37 CFR § 1.56

Applicant notes and acknowledges the obligations cited by the Examiner as to 37 CFR § 1.56. Further comment is deemed unnecessary.

VII. Claims 1, 3 through 6, 19 through 22, 35 and 37 are rejected under 35 USC § 103(a)

The Examiner rejected 1, 3 through 6, 19 through 22, 35 and 37 under 35 USC § 103(a) as unpatentable over Unger in view of Gregoriadis. Applicant respectfully traverses this rejection.

A. Examiner's Rejection:

The Examiner's rejection states that Unger already disclosed a drug delivery system comprising gas-filled liposomes having encapsulated therein a therapeutic drug, wherein at least about 75% or at least about 90% of the therapeutic drug and gas content of the liposomes remain with the liposomes because of their impermeability until they reach the internal region of a patient to be targeted and ultrasound is applied. The Examiner further states that Unger also teaches that the materials which may be utilized in preparing liposomes include any of the materials or combinations thereof known to those skilled in the art as suitable for liposome preparation and the lipid in the gas-filled liposomes may be in the form a single bilayer or a multilamellar bilayer and that utilized lipids to create liposome microspheres include and not limited to lipids such as DMPC, DPPC, DSPC cholesterol, cholesterol sulfate and cholesterol hemisuccinate and if desired a variety of cationic lipids.

The Examiner acknowledges that Unger does not teach specifically the preparation of a liposome comprising saturated synthetic phosphatidyl cholines selected from the group consisting of DMPC, DPPC and DSPC; cholesterol and/or derivatives with a percentage ranging from about 35 to about 50 mole-%, cationic lipids selected from the group of DC-Chol, DAC-Chol, DMTAP, DPTAP and DOTAP with a percentage ranging from about 5 to 20 mole-% and one or more selected from the group consisting of protein and peptide active substances.

The Examiner believes that the deficiencies in Unger, acknowledged above, in arriving at Applicant's claimed invention are cured by Gregoriadis. The Examiner reasons that Gregoriadis already disclosed at least a liposome preparation comprising at least a cationic compound such as DOTP or DC-Chol, at least one zwitterionic phospholipids such as DPPC and DSPC and cholesterol, wherein the amount of cationic compound is preferably in the range of 5 to 50% of the total moles of liposome forming components. The Examiner further stated that Gregoriadis teaches that the product liposomes may be multilamellar or unilamellar vesicles.

B. Applicants' Claimed Invention: As noted above, Applicant's claimed invention is

to a depot system with burst release avoiding delayed release. Furthermore, as described in amended independent Claims 1 from which claims 3 through 6, 19 through 22, 35 and 37 depend, now requires (i) gas-free liposomes and (ii) depot system having “saturated synthetic phosphatidyl cholines selected from one or more from the group consisting of dimyristoyl phosphatidylcholine (DMPC), dipalmitoyl phosphatidylcholine (DPPC) and distearoyl phosphatidylcholine (DSPC), cholesterol and/or derivatives with a percentage ranging from about 35 to about 50 mole-%, cationic lipids selected from the group of 3-β-[N-(N',N'-dimethylaminoethane)carbamoyl]cholesterol (DC-Chol), 3-β-[N-(N',N'-dimethylaminoethane)carbamoyl]cholesterol (DAC-Chol), N-[1-(2,3-dimyristoyloxy)propyl]-N, N, N-trimethylammonium salt (DMTAP), N-[1-(2,3-dipalmitoyloxy)propyl]-N, N, N-trimethylammonium salt (DPTAP) and N-[1-(2,3-di oleoyloxy)propyl]-N, N, N-trimethylammonium salt (DOTAP) with a percentage ranging from 5 to 20 mole-% in the liposomal membrane, and one or more selected active substances from the group consisting of protein and peptide active substances.”

C. Teachings of Cited References:

Unger: Unger discloses a burst release system incompatible with the claimed burst release avoiding delayed release depot system. Unger's gas-filled liposome compositions and drugs encapsulated therein are employed with ultrasonic energy interacts with a gas within a gas-filled microspheres resulting in a burst of the microspheres. This results in immediate therapeutic agent released without the possibility of any extended release. Unger teaches only a one shot release.

As to specific components, we note that the examples contained within Unger liposomes from DPPC or DPPC/DOTMA or PEG-DPPE or eggPC/DOTMA or DPPC/sodium lauryl sulphate or DSPC were used. Unlike the instant claimed invention, the disclosed specific liposome compositions of Unger do not comprise cholesterol and the presence of cationic lipids is not mandatory. Furthermore Unger teaches the materials that may be utilized in preparing liposomes include any of the materials or combinations thereof known to those skilled in the art as suitable for liposome preparation.

Gregoriadis: Gregoriadis discloses oral vaccines comprising a nucleic acid coding for an antigen against which vaccination is desired. Gregoriadis found that liposomal compositions as oral vaccines preferably comprising at least one zwitterionic phospholipid and at least one

cationic compound. In a preferred aspect of the invention the zwitterionic phospholipid is a mixture of DSPC and DOPE, a saturated phosphatidylcholine and an unsaturated phosphatidylethanolamine (col. 3, line 15-18). Gregoriadis also mentioned that other components may be included in the liposome forming component, such as cholesterol in amounts up to 50 % by weight. However, Gregoriadis teaches that the liposome forming components are preferably free of cholesterol (see col.4, line 18-19 or Example 2 (col. 8, line 67 – col. 9, line 1-3). Accordingly, the liposomal compositions of Gregoriadis are free of cholesterol.

D. Deficiencies of the References:

Unger: Unger is a burst release system and not a burst release avoiding delayed release system. Unger offers no more than a generic disclosure of lipids suitable to make liposomes and drugs encapsulated therein. In the context of the earlier § 102(a) rejection, the Examiner presents Unger and quotes col.7, lines 42-44:

“materials which may be utilized in preparing liposomes include any of the materials or combinations thereof known to those skilled in the art as suitable for liposome preparation.” (emphasis in original) Office Action of May 1, 2009, page 5, last paragraph.

This general statement is followed by a partial quotation from Unger col. 7, line 55 through col. 8, line 32. Applicant sets forth that section of Unger in full:

Lipids which may be used to create liposome microspheres include but are not limited to: lipids such as fatty acids, lysolipids, phosphatidylcholine with both saturated and unsaturated lipids including dioleoylphosphatidylcholine; dimyristoylphosphatidylcholine; dipentadecanoylphosphatidylcholine, dilauroylphosphatidylcholine, dipalmitoylphosphatidylcholine; distearoylphosphatidylcholine; phosphatidylethanolamines such as dioleoylphosphatidylethanolamine; phosphatidylserine; phosphatidylglycerol; phosphatidylinositol, sphingolipids such as sphingomyelin; glycolipids such as ganglioside GM1 and GM2; glucolipids; sulfatides; glycosphingolipids; phosphatidic acid; palmitic acid; stearic acid; arachidonic acid; oleic acid; lipids bearing polymers such as polyethyleneglycol, chitin, hyaluronic acid or polyvinylpyrrolidone; lipids bearing sulfonated mono-, di-, oligo- or polysaccharides; cholesterol, cholesterol sulfate and cholesterol hemisuccinate; tocopherol hemisuccinate, lipids with ether and ester-linked fatty acids, polymerized lipids, diacetyl phosphate, stearylamine, cardiolipin, phospholipids with short chain fatty acids of 6-8 carbons in length, synthetic phospholipids with asymmetric acyl chains (e.g., with one acyl chain of 6 carbons and another acyl chain of 12 carbons), 6-(5-cholesten-3.beta.-yl-oxo)-1-thio-.beta.-D-galactopyranoside, digalactosyldiglyceride, 6-(5-cholesten-3.beta.-yl-oxo)hexyl-6-amino-6-deoxy-1-thio-.beta.-D-galactopyranoside, 6-(5-cholesten-3.beta.-

xyloxy)hexyl-6-amino-6-deoxyl-1-thio-.alpha.-D-manno pyranoside, 12-(((7'-diethylaminocoumarin-3-yl)carbonyl)methylamino)-octadecanoic acid; N-[12-(((7'-diethylaminocoumarin-3-yl)carbonyl)methyl-amino) octadecanoyl]-2-aminopalmitic acid; cholesteryl)4'-trimethyl-ammonio)butanoate; N-succinyl dioleoyl phosphatidylethanolamine; 1,2-dioleoyl-sn-glycerol; 1,2-dipalmitoyl-sn-3-succinylglycerol; 1,3-dipalmitoyl-2-succinylglycerol; 1-hexadecyl-2-palmitoyl glycerophosphoethanolamine and palmitoylhomocysteine, and/or combinations thereof.

If desired, a variety of cationic lipids such as DOTMA, N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride; DOTAP, 1,2-dioleoyloxy-3-(trimethylammonio)propane; and DOTB, 1,2-dioleoyl-3-(4'-trimethyl-ammonio)butanoyl-sn-glycerol may be used. In general the molar ratio of cationic lipid to non-cationic lipid in the liposome may be, for example, 1:1000, 1:100, preferably, between 2:1 to 1:10. . . Unger col. 7, line 55 through col. 8, line 32.

Advancing this wholesale litany of possible liposomal constituents is an improper basis for rejection. Unger represents the archetypal non-obviating “basket disclosure.” *In re Ruschig*, 343 F.2d 965 (CCPA 1965). Nothing in Unger directs one skilled in the art to the claimed selection of liposome forming agents nor excludes unsuitable agents.

As to unsuitable agents, it is now known in the field of delivery of nucleic acid cargoes, that cationic liposomes cannot safely be administered systemically due to the formation of aggregates and with the negatively charged serum components and unspecific adhesion on cellular surfaces (e.g. in Santel et al., *Gene Therapy* (2006) 13:1222-1234 and Andreaskos et al., *Arthritis and Rheumatism* (2009) 60: 994-1005). It is therefore questionable whether the liposomes provided by Unger would allow the intended use. The examples in Unger do not provide such enablement. Applicant respectfully submits that Unger cannot be read as teaching or suggesting a delayed release depot system. This is also reflected in *Gregoriadis*,

As claimed, the instant liposomes are formed of saturated synthetic phosphatidyl choline selected from one or more from the group consisting of dimyristoyl phosphatidylcholine (DMPC), dipalmitoyl phosphatidylcholine (DPPC) and distearoyl phosphatidylcholine (DSPC), cholesterol and/or derivatives with a percentage ranging from about 35 to about 50 mole-%, cationic lipids selected from the group of 3-β-[N-(N',N')-dimethylaminoethane)carbamoyl]cholesterol (DC-Chol), 3-β-[N-(N',N'-

dimethylaminoethane)carbamoyl]cholesterol (DAC-Chol), N-[1-(2,3-dimyristoyloxy)propyl]-N, N, N-trimethylammonium salt (DMTAP), N-[1-(2,3-dipalmitoyloxy)propyl]-N, N, N-trimethylammonium salt (DPTAP) and N-[1-(2,3-dioleoyloxy)propyl]-N, N, N-trimethylammonium salt (DOTAP) with a percentage ranging from 5 to 20 mole-% in the liposomal membrane.

The disclosed specific liposome compositions of Unger do not comprise cholesterol and the presence of cationic lipids is not mandatory. The instant claimed invention comprises saturated phospholipids, such as DSPC, DPPC or DMPC and cholesterol or derivatives and cationic lipids such as DC-Chol, DAC-Chol, DMTAP, DPTAP and/or DOTAP, which are useful as delayed release depot systems for the sustained release of active agents. This is inconsistent with the teaching of Unger. Here, the presence of cationic lipid is mandatory.

Separately or combined, the teachings of Unger and Gregoriadis do not reach the claimed delayed release depot system absent improper picking and choosing and improper hindsight reconstruction of Applicant's invention. Applicant respectfully requests that the rejected claims be withdrawn.

Conclusion

Applicant believes that the foregoing response has placed the application in condition for allowance which is promptly requested.

One new independent claim has been added, for a total of three independent claims. Please charge any deficiency as well as any other fees which may become due at any time during the pendency of this application, or credit any overpayment of such fees to deposit account No. 02-3038. Also, in the event any extensions of time for responding are required for the pending

application, please treat this paper as a petition to extend the time as required and charge Deposit Account No. 02-3038.

Respectfully submitted,

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